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Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study

*WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**

Summary

Background The association between oral contraceptive (OC) use and acute myocardial infarction (AMI) was established in studies from northern Europe and the USA, which took place during the 1960s and 1970s. Few data are available to quantify the risk worldwide of AMI associated with use of OCs introduced since those early studies. This hospital-based case-control study examined the association between a first AMI and current OC use in women from Africa, Asia, Europe, and Latin America (21 centres).

Methods Cases were women aged 20–44 years who had definite or possible AMI (classified by history, electrocardiographic, and cardiac-enzyme criteria), who were admitted to hospital, and who survived for at least 24 h. Up to three hospital controls matched by 5-year age-band were recruited for each of the 368 cases (941 controls). All participants were interviewed while in hospital with the same questionnaire, which included information on medical and personal history, lifetime contraceptive use, and blood-pressure screening before the most recent episode of OC use. Odds ratios compared the risk of AMI in current OC users and in non-users (past users and never-users combined).

Findings The overall odds ratio for AMI was 5·01 (95% CI 2·54–9·90) in Europe and 4·78 (2·52–9·07) in the non-European (developing) countries; however, these risk estimates reflect the frequent coexistence of other risk factors among OC users who have AMI. Very few AMIs were identified among women who had no cardiovascular risk factors and who reported that their blood pressure had been checked before OC use; odds ratios associated with OC use in such women were not increased in either Europe or the developing countries. Among OC users who smoked ten or more cigarettes per day, the odds ratios in Europe and in the developing countries were over 20. Similarly, among OC users with a history of hypertension (during pregnancy or at any other time), odds ratios were at least ten in both groups of countries. No consistent association between odds ratios for AMI and age of OC users or oestrogen dose was apparent in either group of countries. No significant increase in odds ratios was apparent with increasing duration of OC use among current users, and odds ratios were not significantly increased in women who had stopped using OCs, even after long exposure. The study had insufficient power to examine whether progestagen dose or type had any effect on AMI risk.

Interpretation Current use of combined OCs is associated with an increased risk of AMI among women with known cardiovascular risk factors and among those who have not been effectively screened, particularly for blood pressure. AMI is extremely rare in younger (<35 years) non-smoking women who use OCs, and the estimated excess risk of AMI in such women in the European centres is about 3 per 10^6 woman-years. The risk is likely to be even lower if blood pressure is screened before, and presumably during, OC use. Only among older women who smoke is the degree of excess risk associated with OCs substantial (about 400 per 10^6 woman-years).

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Introduction

Acute myocardial infarction (AMI) was first linked with the use of oral contraceptives (OCs) in a case report[1] shortly after these drugs became available. Thereafter the results of many case-control studies[2–17] suggested that the association was causal, and three cohort studies[18–20] provided limited but supportive information.

Most previous studies of the cardiovascular side-effects of OCs were undertaken in the 1960s and 1970s, and they provide limited information on risks associated with modern OCs, which have low oestrogen doses. Also, few

*Writing committee, study organisation, and participants listed at end of article

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	Number of cases (% of total in region)					Combined (n=384)
	Europe (n=203)	Developing countries				
		All (n=181)	Africa (n=10)	Asia (n=37)	Latin America (n=134)	
Definite	180 (88·7%)	141 (77·9%)	1 (10%)	30 (81%)	110 (82·1%)	321 (83·6%)
Possible	18 (8·9%)	29 (16·0%)	3 (30%)	5 (14%)	21 (15·7%)	47 (12·2%)
Other	5 (2·5%)	11 (6·1%)	6 (60%)	2 (5%)	3 (2·2%)	16 (4·2%)

Table 1: **Distribution of types of AMI by region**

data are available from outside northern Europe and the USA. In the time since most of the previous studies took place, prescribing recommendations have changed towards the preferential use of OCs by younger women who do not have other risk factors for cardiovascular disease. Thus, three case-control studies conducted during the 1990s[15–17] showed only small and non-significant increases in risk of AMI associated with OC use in the UK and USA.

The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception,[21] a multicentre, hospital-based, case-control study carried out in Africa, Asia, Europe, and Latin America (including the Caribbean), was designed to examine the association between use of modern OCs and three cardiovascular diseases. The results of the venous thromboembolism and stroke components of the study have been reported previously.[22–25] This paper reports findings on the AMI component of the study, the principal aim of which was to examine the association between a first AMI and current OC use in women from Europe and from the other three regions combined. Subsidiary aims were to investigate whether risk estimates differed among subgroups of women, such as smokers or women with hypertension, or according to type, duration, and past use of OCs, which most previous studies had been too small to address.

Patients and methods

Detailed description of study methods has been given elsewhere.[21,22] This hospital-based, case-control study was undertaken in 21 centres in 17 countries in Africa, Asia, Europe, and Latin America (including the Caribbean). Each centre recruited cases and controls from a variable number of collaborating hospitals. Women were eligible as cases if they were aged 20–44 years (15–49 in three centres), had been admitted to a collaborating hospital between Feb 1, 1989, and Jan 31, 1995, and had a discharge diagnosis of AMI. We excluded women who died within 24 h of admission, who had a history of stroke, deep-vein thrombosis, pulmonary embolism, AMI, or natural or surgical menopause, or who had a history within the previous 6 weeks of pregnancy, major illness causing bed rest of longer than a week, or surgery.

Case definition

A monitoring system was set up in each centre to identify all eligible cases. A review of the medical history, cardiac enzyme results, and electrocardiograms (ECGs) allowed classification of these cases as definite, possible, or other according to the classification used in the MONICA project.[26] ECGs were coded centrally by a cardiologist who was not aware of the patient's exposure to OCs.

Definite AMI was diagnosed if two or more ECGs showed definitive changes; if ECGs showed probable changes and cardiac enzymes were abnormal (⩾two times the upper limit of the normal range in the collaborating hospital); if symptoms were typical and enzymes were abnormal; or if fresh myocardial

	Europe					Developing countries				
	Cases (n=198)	Controls, by OC use				Cases (n=170)	Controls, by OC use			
		All (n=480)	Current (n=78)	Past (n=264)	Never (n=138)		All (n=461)	Current (n=41)	Past (n=171)	Never (n=249)
Age (years)										
<35	18·7	21·3	28·2	21·2	17·4	20·6	21·7	39·0	16·4	22·5
35–39	26·8	27·5	37·2	27·3	22·5	28·8	30·2	34·2	36·2	25·3
⩾40	54·5	51·2	34·6	51·5	60·1	50·6	48·1	26·8	47·4	52·2
Mean (SD) body-mass index (kg/m²)	26·1* (6·1)	24·8* (4·9)	23·3 (3·2)	25·1 (5·5)	25·2 (4·4)	24·0† (4·3)	23·9† (4·1)	23·6 (3·7)	23·9 (4·1)	23·9 (4·2)
Number of livebirths										
0	11·1	11·9	10·2	9·8	16·7	15·3	13·0	9·8	6·4	18·1
1–2	67·7	71·4	71·8	71·6	71·0	30·0	42·3	51·2	41·5	41·4
⩾3	21·2	16·7	18·0	18·6	12·3	54·7	44·7	39·0	52·1	40·5
Married/stable union	78·3	80·4	84·6	76·5	85·5	73·5	68·6	78·1	74·8	62·7
Education beyond secondary level	21·2	29·6	35·9	34·5	16·7	18·8	13·0	14·6	12·9	12·9
Current smoker‡	77·3	34·8	37·2	35·6	31·9	42·9	24·0	33·2	29·2	18·9
Weekly alcohol consumption ⩾1 unit	20·9	24·0	32·1	27·7	12·3	3·5	3·4	2·4	4·7	2·8
Self-reported history of										
Hypertension§	22·7	5·2	1·3	5·3	7·3	27·7	6·7	0	8·2	6·8
Hypertension during pregnancy¶	19·6	13·2	9·0	15·9	9·4	24·1	9·3	4·9	11·7	8·4
Diabetes mellitus	7·6	1·5	1·3	1·9	0·7	8·8	2·2	0	1·8	2·8
Rheumatic heart disease	1·0	0·2	0	0	0·7	2·4	0·2	0	0·6	0
Abnormal blood lipids	7·4	1·1	1·3	1·5	0	5·3	0·4	0	0	0·8
Family history of										
Stroke	3·6	2·3	3·9	1·5	2·9	8·9	3·3	2·4	2·9	3·6
AMI	12·7	2·9	5·1	3·0	1·5	9·0	1·5	2·4	1·2	1·6

*Unknown in one case and four controls (three past, one current user). †Unknown in 22 cases and 74 controls (40 never, 26 past, 8 current users). ‡Smoked at least one cigarette in the 3 months before illness that caused hospital admission (cases) or before admission (controls). §Diagnosed before current OC use and other than in pregnancy. ¶Blood-pressure problems in pregnancy, including pre-eclampsia and eclampsia.

Table 2: **Characteristics of AMI cases and controls (% unless otherwise stated)**

Region and type of user	Cases	Controls	Odds ratio (95% CI)	
			Crude	Adjusted
Relative to non-user				
Europe				
Non-user	136	402	1·00	1·00*
User	62	78	3·21 (1·94–5·32)	5·01 (2·54–9·90)•
Developing countries				
Non-user	131	420	1·00	1·00†
User	39	41	3·26 (1·94–5·49)	4·78 (2·52–9·07)†
Relative to never-users				
Europe				
Never	44	138	1·00	1·00‡
Past	92	264	1·16 (0·73–1·86)	1·23 (0·67–2·26)‡
Current	62	78	3·59 (1·95–6·60)	5·64 (2·49–12·8)‡
Developing countries				
Never	63	249	1·00	1·00§
Past	68	171	1·56 (1·04–2·33)	1·48 (0·88–2·49)§
Current	39	41	4·04 (2·30–7·09)	6·13 (2·99–12·6)§

*Adjusted for history of hypertension other than in pregnancy, diabetes, body-mass index category, abnormal blood lipids, and smoking categories (never/past/<10/≥10 cigarettes per day); excludes one case (user) and four controls (non-users) with unknown body-mass index. †Adjusted for history of hypertension, diabetes, abnormal blood lipids, number of livebirth categories (0/1–2/≥3), and smoking categories. ‡Adjusted for history of hypertension, diabetes, body-mass index categories, and smoking categories; excludes one case (current user) and four controls (one never-user, three past users) with unknown body-mass index. §Adjusted for history of hypertension, diabetes. abnormal blood lipids, family history of AMI, number of livebirth categories, and smoking categories; excludes three cases (past users) and four controls (three never-users, one past user) with unknown family history of AMI.

Table 3: **Odds ratios for AMI in relation to use of combined OCs by region**

infarction, recent coronary occlusion, or both, were found at necropsy.[26]

Possible AMI was diagnosed when the patient had typical symptoms without any good evidence for an alternative diagnosis, but the ECG and enzyme results did not satisfy the criteria for definite AMI.

Other AMI was used for any remaining cases.

Controls and interviews

For each case, up to three female controls matched by 5-year age-band were recruited as previously described.[21,22] All cases and controls were interviewed in hospital in a standard way with the same questionnaire. The contents of the questionnaire, participation rates, and all relevant study definitions have been outlined elsewhere.[21,22,24]

This report assesses risk of AMI among current users of combined OCs compared with women not currently using OCs. Women who currently used progestagen-only contraceptives (oral: five cases and ten controls; injectable: one case and eight controls) or combined injectable contraceptives (one case and seven controls) were not classified as current OC users. One woman with AMI who was a current OC user but did not know the type was classified as a current user of combined OCs and was included in all analyses except those referring to type of preparation. In the analyses, non-users (past users and never-users combined) were preferred to never-users as the reference group as previously described.[22,24]

Information about hypertension was obtained from responses to four questions: had the respondent ever (other than in pregnancy) had high blood pressure; had she had a blood-pressure problem, including pre-eclampsia or eclampsia, during but not necessarily confined to pregnancy (hypertension in pregnancy); had medication to control high blood pressure been used in the 3 months before the illness that had caused hospital admission; and among OC users, had the blood pressure been checked before the most recent episode of OC use.

13 (3·4%) of the eligible AMI cases were not interviewed because they were too ill or died before the questionaire could be completed. For them, the closest available relative or friend was interviewed as a proxy.[27] Six cases from Germany and their 11 controls were recruited for this study and included in these analyses were inadvertently included in the analysis of a subsequent study, preliminary results of which have been reported.[28]

Statistics

Conditional logistic regression models were fitted and adjusted for confounding by standard methods.[29] In addition, all odds ratios were adjusted for smoking (except in analyses of smoking and all risk factors). The patterns of OC use, risk factors for AMI, and confounding differed in Europe from those in the other three (developing) regions. Consequently, and as planned a priori, separate models were fitted for Europe and for the developing regions combined. Trends of odds ratios in stratified analyses were assessed by a test for linear trend in the log odds ratios.[30]

To compare the AMI risk according to type of progestagen (desogestrel, gestodene, or levonorgestrel), we conducted an analysis restricted to those centres at which there was any use of the newer products.

Cases in the UK came from hospitals that covered a defined geographical area with a known population size stratified for age and sex. Hence, the incidence of hospital-admitted first AMIs satisfying study eligibility criteria in that region could be calculated. With adjustment of this rate for an estimated 35% of patients with AMI who either were not admitted to hospital or died within 24 h of admission[31] and use of prevalence of patterns of OC use and smoking among controls in the European region, we also estimated the incidence rates of AMI among younger (<35 years) and older women by smoking and use of OCs.

Results

Of the 384 AMI cases, 89% in Europe and 78% in the developing countries were classified as definite. ECGs and cardiac enzyme results were available for more than 99% of cases in Europe and 90% in the developing countries. The data were insufficient in 16 women to allow their classification as definite or possible cases (table 1). All subsequent analyses exclude these "other" cases and their controls. The exclusion of the six cases and their controls common to this and a previously reported study[28] did not change risk estimates substantially.

941 controls were matched to the remaining 368 cases, with an average of 2·4 controls per case in Europe and 2·7 in the developing countries. 56·4% of controls in Europe and 61·7% in the developing countries had a diagnosis of trauma, skin disease, appendicitis, or tonsil, sinus, renal, bone, or joint disorder.

Smoking, a history of hypertension (in pregnancy or other than in pregnancy), diabetes, rheumatic heart disease, or abnormal blood lipids, and a family history of stroke or AMI were all more common among cases than controls in both groups of countries, whereas marital status and alcohol intakes were similar in cases and controls (table 2). The mean ages of cases and controls were similar in Europe (38·8 and 38·2 years, respectively) and in the developing countries (38·4 and 37·7 years, respectively); in both groups of countries the majority of cases were 40 years or older. The prevalence of current OC use among cases and controls in Europe (31·3% and 16·3%, respectively) was higher than in the developing countries (22·9% and 8·9%).

The crude odds ratios for AMI in Europe and the developing countries, respectively, were 7·69 (2·17–27·2) and 12·2 (2·61–56·6) for a history of abnormal blood lipids; 10·9 (6·33–18·9) and 5·33 (2·97–9·56) for smoking ten or more cigarettes per day (compared with non-smokers); 5·63 (3·14–10·1) and 5·69 (3·34–9·70) for a history of high blood pressure (detected before the current episode of OC use and not during pregnancy); 5·47 (2·60–11·5) and 5·39 (2·18–13·4) for a family history of AMI; 4·97 (2·00–12·4) and 4·07 (1·82–9·11)

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Exhibit 168

JA-0003336

	Non-users	Users					
	Cases/controls	All		No BP check		BP check	
		Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Europe*							
Age (years)							
All	136/398	59/76	4·56 (2·30–9·06)	32/25	9·47 (3·72–24·1)	27/51	2·60 (1·15–5·89)
<35	17/79	20/21	7·29 (2·22–24·0)	11/8	15·2 (2·97–77·2)	9/13	3·83 (0·88–16·6)
⩾35	119/319	39/55	3·47 (1·47–8·22)	21/17	7·13 (2·24–22·7)	18/38	2·06 (0·75–5·70)
Oestrogen dose							
<50 µg		28/33	4·69 (2·02–10·9)	11/12	7·58 (2·30–24·9)	17/21	3·23 (1·11–9·42)
⩾50 µg		31/43	4·46 (1·98–10·0)	21/13	10·6 (3·44–32·6)	10/30	2·09 (0·71–6·14)
Developing countries†							
Age (years)							
All	131/420	39/40	4·85 (2·55–9·24)	26/19	6·04 (2·77–13·2)	13/21	3·48 (1·39–8·70)
<35	23/83	12/14	4·11 (1·28–13·2)	8/9	4·27 (1·14–16·0)	4/5	3·76 (0·64–22·2)
⩾35	108/337	27/26	5·18 (2·45–11·0)	18/10	7·17 (2·79–18·5)	9/16	3·32 (1·14–9·67)
Oestrogen dose							
<50 µg		13/22	2·93 (1·23–6·97)	8/10	3·46 (1·13–10·7)	5/12	2·33 (0·66–8·26)
⩾50 µg		26/18	7·69 (3·29–18·0)	18/9	9·70 (3·49–27·0)	8/9	5·26 (1·48–18·7)

OR=odds ratio; BP=blood pressure. Reference group=non-users (OR=1). *Adjusted for history of hypertension, diabetes, body-mass index, abnormal blood lipids, and smoking; excludes one case (user) and four controls (non-users) with unknown body-mass index, two cases (users) and two controls (users) with unknown blood-pressure check status. †Adjusted for history of hypertension, diabetes, abnormal blood lipids, number of livebirths, and smoking; excludes one control (user) with unknown blood-pressure check status,

Table 4: **Odds ratios for AMI in relation to current use of combined OCs by age, oestrogen dose, and whether blood pressure was checked before current episode of OC use**

for diabetes; 6·00 (0·54–66·2) and 12·0 (1·34–107) for a history of rheumatic heart disease; 1·48 (0·93–2·37) and 3·50 (2·11–5·80) for hypertension in pregnancy; and 2·13 (0·99–4·59) and 0·82 (0·34–1·99) for a body-mass index of more than 30 kg/m² (compared with less than 20 kg/m²). In Europe, but not in the developing countries, there was a significant inverse relation between highest level of education achieved (none or primary, secondary, tertiary, or university) and risk of AMI ($p<0·001$).

The crude odds ratios for AMI associated with current OC use compared with non-use (past users and never-users combined) were significantly raised in Europe and the developing countries (table 3). After adjustment for confounding variables, odds ratios rose from about 3 to 5 in both groups of countries. When the analysis was restricted to definite AMI cases, adjusted odds ratios associated with OC use were 4·87 (2·35–10·1) in Europe and 5·20 (2·65–10·2) in the developing countries. Odds ratios associated with past use of OCs were not significantly increased in either group of countries.

Odds ratios associated with OC use did not differ significantly between younger and older women (table 4). The use of OCs containing higher doses of oestrogen (⩾50 µg) was associated with higher odds ratios than use

Factor	Europe				Developing countries			
	Non-users		OC users		Non-users		OC users	
	Cases/ controls	Odds ratio (95% CI)	Cases/ controls	Odds ratio (95% CI)	Cases/ controls	Odds ratio (95% CI)	Cases/ controls	Odds ratio (95% CI)
History of hypertension other than in pregnancy (HBP)								
No	96/374	1·00*	45/75	3·85 (1·88–7·89)	84/389	1·00†	28/38	3·66 (1·81–7·39)
Yes	40/24	5·43 (2·39–12·4)	16/3	68·1 (6·18–751)	47/31	9·52 (4·90–18·5)	11/3	15·3 (3·27–71·6)
History of blood-pressure problems in pregnancy (HIP)								
No	106/343	1·00‡	53/71	4·49 (2·19–9·20)	101/379	1·00§	28/39	3·99 (1·98–8·06)
Yes	30/55	0·99 (0·45–2·19)	8/7	10·0 (2·40–42·0)	30/41	1·95 (0·93–4·10)	11/2	23·8 (4·55–124)
Current smoker								
No	29/261	1·00¶	15/49	3·96 (1·52–10·4)	82/323	1·00‖	15/27	4·50 (1·89–10·7)
<10 cigarettes/day	11/23	4·74 (1·65–13·6)	2/13	5·04 (0·78–32·4)	21/63	1·36 (0·69–2·69)	5/5	10·68 (2·49–45·9)
⩾10 cigarettes/day	96/114	11·1 (5·68–21·8)	44/16	87·0 (29·8–254)	28/34	5·62 (2·61–12·1)	19/9	22·6 (7·60–67·2)
Reported risk factor status (HBP, rheumatic heart disease, diabetes, abnormal blood lipids, HIP, or smoking								
No risk factor	16/205	1·00**	10/41	3·07 (1·06–8·95)	37/272	1·00††	11/26	3·99 (1·58–10·1)
At least one	120/193	8·18 (4·33–15·4)	51/37	37·3 (15·2–91·7)	94/148	6·57 (3·86–11·2)	28/15	20·8 (9·14–47·2)

Reference group non-users. All European data exclude one case (user) and four controls (non-users) with unknown body-mass index. *Adjusted for diabetes, body-mass index, abnormal blood lipids, HIP, and smoking categories. †Adjusted for diabetes, abnormal blood lipids, number of livebirths, HIP, and smoking categories. ‡Adjusted for HBP, diabetes, body-mass index, abnormal blood lipids, and smoking categories.§Adjusted for HBP, diabetes, abnormal blood lipids, number of livebirth categories, and smoking categories. ¶Adjusted for HBP, diabetes, body-mass index, and abnormal blood lipids. ‖Adjusted for HBP, diabetes, abnormal blood lipids, and number of livebirth categories. **Adjusted for body-mass index. ††Adjusted for number of livebirths.,

Table 5: **Odds ratios for AMI in relation to current use of combined OCs according to other risk factors**

	Non-users		Users					
	Cases/controls	OR (95% CI)	All		No BP check		BP check	
			Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Europe†								
Non-smokers	16/205	1·00	9/40	4·47 (1·27–15·7)	7/11	16·4 (3·08–87·7)	2/29	1·10 (0·12–9·69)
Smokers	53/113	8·02 (3·54–18·2)	37/26	41·3 (12·5–136)	20/12	71·4 (16·5–309)	17/14	26·6 (7·00–101)
Developing countries‡								
Non-smokers	34/229	1·00	9/19	5·95 (1·47–24·1)	7/8	9·64 (1·95–47·8)	2/11	1·10 (0·09–12·9)
Smokers	21/68	2·19 (0·94–5·08)	14/11	21·0 (4·93–89·1)	11/8	31·0 (5·39–178)	3/3	9·08 (0·88–93·2)

BP=blood pressure; OR=odds ratio. *Low-risk women=no history of hypertension other than in pregnancy, diabetes, rheumatic heart diseases, abnormal blood lipids, or hypertension in pregnancy. †Adjusted for body-mass index; excludes one case (user) and four controls (non-users) with unknown body-mass index, and two cases (users) and two controls (users) with unknown BP check status. ‡Adjusted for number of livebirths and body-mass index; excludes one control (user) with unknown BP check status, 13 cases (eight non-users, five users) and 65 controls (57 non-users, eight users) with unknown body-mass index.

Table 6: **Odds ratios for AMI associated with current use of combined OCs among low-risk women* by reported blood-pressure check before current episode of OC use and smoking status**

of lower-dose OCs in the developing countries but not in Europe. In Europe and in the developing countries, odds ratios were consistently higher among women who reported that their blood pressure was not checked before the current episode of OC use, irrespective of age or oestrogen dose (table 4).

All three cases and five controls who currently used OCs containing desogestrel or gestodene were from the UK (three cases, four controls) or Germany (one control). In these two countries, the estimated risk of AMI (matched, adjusted for smoking) for users of these OCs compared with non-users was 0·97 (0·14–6·96), whereas that among users of low-oestrogen-dose OCs containing levonorgestrel was 1·64 (0·49–5·54) based on 13 cases and 17 controls. However, all eight users of OCs containing desogestrel or gestodene reported that their blood pressure had been checked before the current episode of OC use, whereas only six cases and 11 controls who used low-dose levonorgestrel-containing OCs reported a blood-pressure check. Risk estimates for AMI among women who reported blood-pressure checking were almost identical for users of OCs containing desogestrel or gestodene and users of levonorgestrel-containing OCs.

Compared with non-users of OCs who had no history of high blood pressure other than in pregnancy, odds ratios associated with OC use, irrespective of reported blood-pressure check status, were increased among women who also reported a history of high blood pressure, especially pronounced in Europe (table 5). In addition, compared with women who did not use OCs and had no history of hypertension in pregnancy, the risk estimates associated with OC use in both groups of countries were increased among those who also reported a history of hypertension in pregnancy. Furthermore, this effect was also apparent among women whose blood-pressure problems were confined to pregnancy (data not shown).

	Incidence per 10^6 woman-years		Attributable risk
	Non-users of OCs	Users of OCs	
Women <35 years			
Non-smokers	0·83	3·56	2·73
Smokers	7·78	42·7	34·9
Women ⩾35 years			
Non-smokers	9·45	40·4	31·0
Smokers	88·4	484·6	396·2

Table 7: **Estimated incidence rates and attributable risks per 10^6 woman-years associated with current OC use by age and smoking status among European women**

Compared with non-smoking non-users of OCs, current smoking increased the odds ratios associated with OC use and showed a dose-response effect on risk estimates among both OC users and non-users (table 5). The odds ratio among the five non-smoking cases and their controls in Europe who reported a blood-pressure check before the episode of OC use was 1·34 (0·34–5·34); the corresponding odds ratio in the developing countries (five cases of this type) was 2·66 (0·81–8·79).

Table 5 also shows odds ratios associated with OC use among those apparently with and without any of the standard cardiovascular risk factors compared with non-users of OCs with none of these risk factors. Although odds ratios among women without risk factors were increased, the combination of at least one risk factor with OC use greatly increased the odds ratio. In Europe, 87% of cases and 48% of controls had at least one risk factor for cardiovascular disease; of the 62 cases among OC users, only 11 had no risk factors (one case was excluded from this analysis). In the developing countries, 72% of cases and 35% of controls had at least one cardiovascular risk factor; of the 39 cases among OC users, 11 had no other risk factor.

Table 6 shows the large impact of smoking and reported blood-pressure checking on odds ratios associated with current OC use among women with no other cardiovascular risk factors. Among women of this category who did not smoke, only three of nine OC-using cases in Europe and three of nine in the developing countries (one case was excluded from each group in table 6) reported having had a blood-pressure check, whereas 29 of 40 and 11 of 19 OC-using controls in Europe and the developing countries, respectively, reported a blood-pressure check. Although confidence intervals were wide, odds ratios were not increased among those very few women without other risk factors who did not smoke and who reported a blood-pressure check before the current episode of OC use.

Among current users of OCs, duration of lifetime use and of current episode of OC use did not affect risk estimates of AMI (data not shown), and no significant increase in risk was apparent among past users (table 3). In Europe, the odds ratios among past users who had used OCs for 10 years or more was 1·61 (0·62–4·16).

The incidence of hospital-admitted first AMI meeting study eligibility criteria in the Oxford region was 18 per 10^6 woman-years during the course of the study. After allowance for cases who were not admitted to hospital or who died within 24 h of admission,[31] this rate increased

to 27 per 10^6 woman-years. The estimated incidence was 7·6 per 10^6 woman-years for women younger than 35 years and 58 per 10^6 woman-years for those aged 35 years or older. With the assumption that patterns of smoking and OC use were the same as in all European countries, the estimated annual incidences by age, smoking, and OC use are shown in table 7. These results show the major adverse impact of age and smoking on the excess or attributable risks associated with OC use.

Discussion

Risk estimates for AMI associated with current OC use are substantially modified by the presence of other cardiovascular risk factors, and very few cases of AMI were identified among OC users who had no such risk factors and who reported a blood-pressure check before the current episode of OC use. Although current use of combined OCs was associated overall with a significantly increased risk of a first AMI, with adjusted odds ratios of about five in Europe and the developing countries, this association appears to result from high rates of coexistent risk factors and inadequate screening among OC users, which may have resulted in incomplete information and unmeasured confounding. Overall risk estimates in this study are higher than those observed in most previous studies,[20] particularly three recent smaller studies from the UK[15] and the USA.[16,17] However, this discrepancy may well be the result of differences in the prevalence of risk factors for AMI and in OC use patterns among the countries included in the various studies. For example, compared with other countries included in the WHO study, in the UK and the USA, OCs are used less frequently by women with other cardiovascular risk factors, and in these countries blood pressure is routinely checked before OCs are prescribed. In our study the odds ratio associated with OC use in the UK was 2·10 (0·63–7·07); that among non-smoking women who reported a blood-pressure check before the current episode of OC use was closer to unity and compatible with the other recent studies, although the confidence intervals were wide.

The large increases in odds ratios after adjustment for confounders confirms that, with the exception of smoking in the developing countries, OCs were used less by women who had other risk factors for cardiovascular disease; this finding particularly applied to those with a history of hypertension (both groups of countries), and to those with a high body-mass index (Europe). The two largest contributors to the 56% increase in the odds ratio in Europe after adjustment were a history of hypertension and body-mass index. In the developing countries the two major confounders were a history of hypertension (59% increase in odds ratios after adjustment) and smoking (26% reduction in odds ratios).

The lack of a consistent effect of age on odds ratios in this study is compatible with previous findings.[32] However, because of the steep rise in incidence of AMI with age the attributable risk associated with OC use is much greater among older women (table 7).

Data from the developing countries support the findings of some studies[33] that OC-associated risk of AMI was higher with higher oestrogen doses. However, in keeping with most other studies,[7,11] no such effect was seen in the European centres. There were no important differences in characteristics of users of OCs with low and higher oestrogen doses in the two groups of countries that could explain the apparently inconsistent oestrogen-dose effect. The study had insufficient power to investigate whether for a given oestrogen dose, the dose of progestagen had a major impact on risk of AMI,[33] or to assess any differences in risk according to type of progestagen. The very limited information from this study on any differences in AMI risk associated with the use of OCs containing desogestrel or gestodene and levonorgestrel is compatible with large differences between these products in either direction and hence no useful conclusions can be drawn from our data.

The dose-response effect of increasing smoking categories on OC-associated risk (table 5) is in keeping with the findings of several previous studies.[34,35] The possibility of a synergistic effect between these two risk factors, as suggested by the odds ratios among European women, has also been reported previously.[34,35] However, in contrast to some previously published data,[19,28] odds ratios associated with OC use were also significantly raised among non-smokers (table 5), although in non-smokers with no other risk factors and reported blood-pressure checking, odds ratios were not increased (table 6).

Univariate analyses confirmed the established role of hypertension as a major risk factor for AMI, and the effect of high blood pressure during pregnancy and other than in pregnancy on OC-associated risk of AMI was clearly shown (table 5). These data also suggest the possibility of a synergistic effect between high blood pressure and OC use on risk of AMI. The influence of blood pressure on OC-associated risk was further emphasised by the higher odds ratios among women who did not have a blood-pressure check before the current episode of OC use (table 4), which was apparent in parts of Latin America and all European centres except the UK, where blood pressure was checked routinely before OC prescription. Whether the lower OC-associated risk in women who reported a blood-pressure check before the current episode of OC use purely relates to screening for increased blood pressure or also reflects other aspects of health care or health-care-seeking behaviour is unclear. In the developing countries, where 69% of cases and 42% of controls acquired their OCs from a non-clinical source (eg, family, shop, or friend), the adjusted odds ratio associated with OCs was 2·34 (0·94–5·83) for those obtained from a clinical source (eg, family planning clinic, hospital, or family doctor) and 7·90 (3·58–17·4) for those obtained from a non-clinical source. The equivalent calculation was not possible in Europe because OCs had been supplied through a clinical outlet to all controls and to all but two cases who were current OC users.

With the exception of one of the largest case-control studies of AMI and OC use,[10] past use of OCs has not been shown to be associated with increased risk of AMI. In our study, odds ratios among past users were 1·23 (0·67–2·26) in Europe and 1·48 (0·88–2·49) in the developing countries. In contrast to the findings of Slone and colleagues,[10] past users in Europe who had used OCs for 5–10 years and for 10 years or more did not have significantly increased odds ratios (1·22 [0·53–2·83]) and 1·61 [0·63–4·16], respectively). Similarly, and consistent with one previous report,[18] no duration effect of OC use on AMI risk was apparent among current OC users.

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Possible sources of bias

The validity of AMI cases included in previous case-control studies has been questioned in one review.[36] In our study, the majority of cases in both groups of countries were classified as definite cases according to standard criteria, and odds ratios among these definite cases were similar to those among all cases included in analyses.

Possible bias introduced by inclusion of data from proxy respondents for AMI cases has been investigated and reported elsewhere.[27] That assessment showed that information from proxy respondents was reliable for current OC use, and that the estimated impact of misclassification by the 3·4% of AMI cases for whom a proxy respondent was used on overall risk estimates was less than 1%.[27]

A potential limitation of this study was that cases were restricted to those who survived at least 24 h after hospital admission. Included cases may not therefore have been representative of all AMI cases, about 35% of whom die within 24 h.[31] However, symptomatic non-fatal AMI in young women almost always results in hospital admission and, although validation of the low reported refusal rates among cases and controls was not possible in all centres, regular reviews of hospital discharge data confirmed high participation rates. Hence, the results reported here should at least be applicable to almost all AMIs that are not rapidly fatal in young women.

Detailed information was obtained on OC exposure from cases and controls who were interviewed under similar conditions in hospital and were not aware of the main objective of the study. The use of samples and pictures of locally available OCs, and the comprehensive history of OC use permitted detailed investigation of all types and patterns of OC use. Biased recall of OC exposure could have occurred as a result of the severity of AMI compared with the control diagnoses and the knowledge of cardiovascular risk associated with OCs. The impact of such a potential bias cannot be assessed because contraceptive history was not validated against medical records or prescriptions. However, any such bias is more likely to relate to past rather than current OC use—which was the primary exposure investigated in this study. An exaggerated estimate of risk associated with OC use could also have occurred if controls stopped taking OCs in anticipation of hospital admission so that they were classified as past and not current OC users. However, only 0·3% of non-user controls from Europe and 0·2% of those from the developing countries had stopped OC use more than 3 months before hospital admission for this reason, and were thus classified as past rather than current OC users.

Balancing risks

The estimated incidence rates of AMI in Europe based on data from the Oxford region of the UK (table 7) show that AMI in non-smoking women of reproductive age who use OCs is a rare event; incidence rates rise appreciably above 4 per 100 000 per year only among OC users who smoke. Consequently, in this population the excess or attributable risk estimates associated with use of OCs among women who do not smoke were between 2·5 and 35 per 10^6 woman-years depending on age; the corresponding estimates among smokers were between 30 and 400 per 10^6 woman-years. Furthermore, the excess AMI incidence due to OC use (which is small except among older smokers) is likely to be even smaller if appropriate screening, particularly of blood pressure, is carried out before and during OC use.

Although the overall odds ratios for AMI associated with OC use, even among women without known risk factors, are higher than shown in most previous studies, risk estimates were substantially lower among those who reported that their blood pressure had been checked before OC use. The risks among such women are compatible with the lower risk estimates found in the Oxford region of the UK in this study and those reported in countries where blood-pressure screening before OC use is routine.[15-17] The higher odds ratios observed in the WHO study probably reflect more frequent use of OCs by women with other cardiovascular risk factors and less screening than is currently carried out in, for example, the UK and the USA. They therefore represent risk estimates associated with OC use among women, an unknown proportion of whom were inadequately screened and had undetected (and hence unrecorded) risk factors. This would inflate the apparently OC-associated risk estimates.

Finally, even with the odds ratios observed in this study, we should emphasise that except among older women who smoke, the absolute risk of an AMI in this age group is very small. The very small excess risk due to OCs should be balanced against the risks and benefits associated with alternative forms of contraception and of the effect of OCs on other cardiovascular endpoints, on protection against certain forms of neoplasia,[37] on quality of life, and ultimately on overall morbidity and mortality.

WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Study Organisation

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